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Laparoscopic Hyperthermic Intraperitoneal Chemotherapy is Safe for Patients with Peritoneal Metastases from Gastric Cancer and May Lead to Gastrectomy

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ABSTRACT

Background. Laparoscopic hyperthermic intraperitoneal chemotherapy (LS-HIPEC) is a novel strategy for patients with gastric adenocarcinoma (GA) metastatic to the peritoneum. We evaluated the safety profile of LS-HIPEC for patients with positive peritoneal cytology (PPC) or carcinomatosis from GA.

Methods. Outcomes were reviewed of patients with stage IV GA with peritoneal involvement who received LS-HIPEC from June 2014 to January 2017. LS-HIPEC included a 60-minute perfusion of mitomycin-C (30 mg) and cisplatin (200 mg) with inflow temperatures of 41–42 °C and outflow temperatures of 39–40 °C.

Results. A total of 71 LS-HIPEC procedures were performed in 44 patients. At diagnosis, 68% (n = 30) had carcinomatosis and 32% (n = 14) had isolated PPC. Three patients (7%) underwent LS-HIPEC for intractable ascites. All patients initially received systemic chemotherapy, and 20 patients (45%) received pre-procedural chemoradiotherapy. The median number of LS-HIPEC procedures performed per patient was one (range 1–5 procedures). There were no conversions to laparotomy, two outflow catheter obstructions, and one major (Clavien-Dindo grade III) surgical complication within 30 days. A total of seven postoperative adverse hematologic events (> CTCAE 2) were observed in five patients (11%), without any major renal or gastrointestinal adverse events within 30 days. The median overall length of hospital stay after LS-HIPEC was 2 (range 2–11) days. Eleven patients (25%) underwent secondary gastrectomy following resolution of peritoneal cytology.

Conclusions. Laparoscopic HIPEC is a safe procedure and may be repeated in patients with peritoneal metastases from gastric cancer. Future studies are required to determine the optimal HIPEC regimen and timing relative to systemic therapy to best minimize morbidity.

In western populations, most gastric cancer patients present with stage IV disease, resulting in a median overall survival of less than 12 months.[1] However, many of these patients have metastatic disease limited to the peritoneal cavity or low-volume carcinomatosis. Current national comprehensive cancer network (NCCN) guidelines recommend systemic chemotherapy or best supportive care for these patients.[2,3] However, effective chemotherapy delivery to the peritoneum is difficult, with the peritoneal-plasma barrier often reported as a limitation to systemic cytotoxic chemotherapy.[4,5] Because of this, regional therapies such as cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are attractive alternatives. Application of chemotherapy directly to the tumor, utilization of higher doses than can be tolerated systemically, and the synergistic effects of

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chemotherapy and heat are advantages of HIPEC that may benefit patients with stage IV gastric adenocarcinoma limited to the peritoneal cavity.[6,7] Benefits of HIPEC, including increases in survival, for patients with stage IV gastric adenocarcinoma are underreported, and therefore current national guidelines do not include HIPEC as a standard of care treatment modality.

While HIPEC performed in conjunction with CRS has a considerable incidence of morbidity and mortality, laparoscopic HIPEC has demonstrated a good safety profile in preliminary and retrospective studies.[8] We recently completed a phase II trial (NCT02092298) of 19 patients to assess the efficacy and safety of laparoscopic HIPEC without CRS in gastric cancer patients with low-volume peritoneal disease, defined as radiologically occult peritoneal carcinomatosis or positive peritoneal cytology only. Based on these early favorable results, we have incorporated the option of laparoscopic HIPEC into our multidisciplinary treatment program for patients with peritoneal metastasis from gastric cancer and begun a more aggressive trial of cytoreduction, HIPEC, and gastrectomy (NCT02891447).[9]

The application of laparoscopic HIPEC for patients with low-volume peritoneal disease is advantageous, because it may be repeated in an attempt to clear peritoneal disease and thus afford patients with traditionally inoperable disease an opportunity for resection. Early outcomes have demonstrated this to be a safe, rational strategy; however, detailed analysis of perioperative complications of laparoscopic HIPEC has not been reported. Therefore, we aimed to characterize the morbidity and toxicity of laparoscopic HIPEC in patients with low-volume peritoneal disease from gastric adenocarcinoma.

METHODS

Study Population

We retrospectively reviewed the records of all patients with a history of gastric or gastroesophageal junction adenocarcinoma metastasis limited to the peritoneum treated with laparoscopic HIPEC at The University of Texas MD Anderson Cancer Center from June 2014 to January 2017. Included in this study are 19 patients from a previous phase II trial (ClinicalTrials.gov: NCT02092298) performed at our institution for patients with cytology positive (CY1) or radiologically occult peritoneal disease (P1). In general, laparoscopic HIPEC is considered at our institution for patients with a histological diagnosis of gastroesophageal junction or gastric adenocarcinoma with CY1 or low-volume P1 disease documented by staging laparoscopy or laparotomy, no other sites of metastasis, Eastern Cooperative Oncology Group performance status ≤ 2, adequate renal function (serum creatinine ≤ 1.5 mg/dL), adequate hematological function (leukocytes $> 2000/\mu L$, neutrophils $> 1200/\mu L$, platelets $> 100{,}000/\mu L$), and adequate hepatic function (aspartate transaminase and alanine transaminase ≤ 5 times the institutional upper limit of normal). HIPEC is considered palliative in patients with intractable ascites who are not being considered for gastrectomy in the future. Patients are ineligible for HIPEC if they have significant heart disease (unstable angina or New York Heart Association class ≥ 2), serious infections, or are pregnant. This retrospective study was approved by the Institutional Review Board of M.D. Anderson Cancer Center.

Multidisciplinary Treatment

All patients were treated with first-line chemotherapy before consideration for laparoscopic HIPEC. All cases were presented in a multidisciplinary gastric cancer conference that included medical oncologists, radiation oncologists, and surgical oncologists. HIPEC was conducted at a minimum of 3 weeks after the last dose of systemic chemotherapy. Preoperative chemotherapy regimens included 5-fluorouracil/oxaliplatin, 5-fluorouracil/oxaliplatin/paclitaxel, or epirubicin/cisplatin/5-fluorouracil. HIPEC could be repeated up to 5 times, with no less than 3 weeks between procedures. Our current multidisciplinary treatment algorithm for patients with P1 or CY1 gastric cancer is shown in Fig. 1.

Laparoscopic HIPEC Technique

Diagnostic laparoscopy was performed at the beginning of all laparoscopic HIPEC procedures with a three-port technique, and peritoneal washings and biopsies of any peritoneal abnormalities were obtained. Two indwelling catheters were placed into the abdominal cavity under laparoscopic visualization through the lateral ports and then secured to the skin after removal of the trocars. The inflow catheter (AViD Dual Stage Venous Drainage Cannula, 29/37 Fr; Edwards Lifesciences, Irvine, CA) was placed into the left upper quadrant. The outflow catheter (polyurethane tube, 24-Fr external/19-Fr internal caliber, with hand-crafted holes) was inserted through the right trocar over the right lobe of the liver. The gastrohepatic ligament and lesser sac are not routinely entered to prevent difficulty at future gastrectomy. The bowel is not routinely run in its entirety.

Once the catheters were in place, a preliminary flow infusion with Plasma-Lyte A solution (pH 7.4; Baxter, Deerfield, IL) was started, and the abdomen was manually agitated. At this point, 30 mg of mitomycin C and 200 mg of cisplatin were added to the circuit. The total volume was

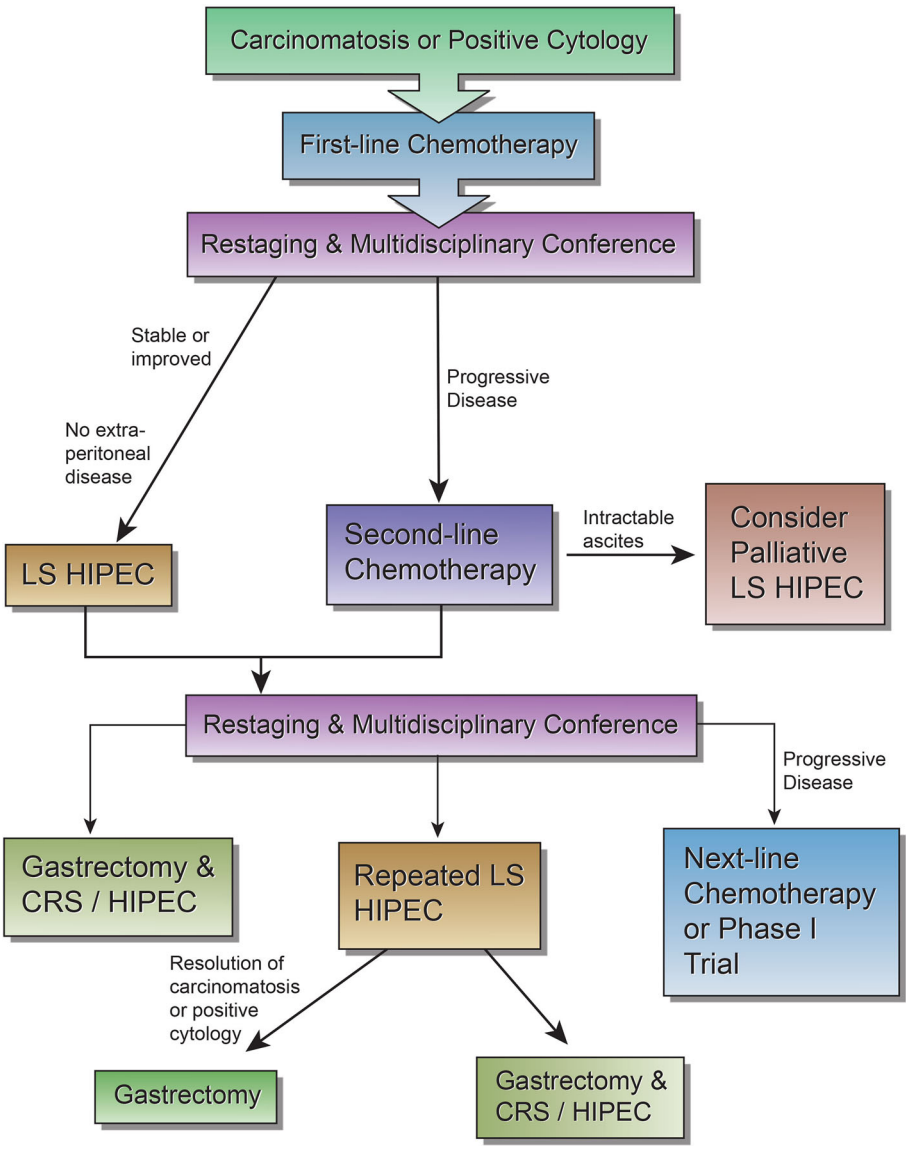

FIG. 1 Proposed integration of LS-HIPEC into the care algorithm for patients with gastric adenocarcinoma metastatic to the peritoneum

raised to 3–7 L to obtain a constant inflow-outflow cycle (flow rate of 700–1500 mL/minute). HIPEC was administered for 60 min, with an inflow temperature of 41–42 °C and an outflow temperature of 39–40 °C. At the end of the procedure, an abdominal washout was performed with 3 L of crystalloid solution. The inflow and outflow cannulas were removed under direct vision, and residual fluid was aspirated. During the procedure, sodium thiosulfate was administered intravenously at a loading dose of 7.5 g/m^2 approximately 20 min before the intraperitoneal perfusion and then at a maintenance dose of 25.56 g/m^2 for 12 h postoperatively.

Data Collection and Safety Outcomes Definitions

Preoperative, intraoperative, and postoperative data were collected from electronic medical records. Additional follow-up by correspondence with the patients and their primary physicians or oncologists was performed. The primary outcome measures for this study were 30-day morbidity and mortality. Surgical complications were graded by the Clavien-Dindo classification system and reported as major (grade III and IV complications) or death (grade V).[10] Adverse events related to the drugs used in HIPEC were classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistics

Data were calculated both per patient and per procedure (measures were repeated for patients who underwent more than one HIPEC). Continuous variables were summarized using means and standard deviations or median and ranges,

as appropriate. Adverse events were reported as numbers of events and percentages.

RESULTS

Patients

Patient demographics and procedural characteristics are detailed in Table 1. A total of 44 patients underwent 71 LS-HIPEC procedures during the study period, and the median number of procedures per patient was 1 (range 1–5). All patients underwent preoperative chemotherapy for a median of 8 cycles (range 3–53) before undergoing LS-HIPEC, whereas 45% of patients underwent preoperative chemoradiation. Specifically, 43 patients received a range of 3 to 17 cycles of preoperative chemotherapy, whereas 1 patient received 53 cycles.

The majority of patients underwent LS-HIPEC for low-volume peritoneal carcinomatosis discovered at staging laparoscopy (68%; Table 1). Three patients underwent LS-HIPEC for malignant ascites. The median length of stay following LS-HIPEC was 2 days (range 2–11).

Procedural Complications and Perioperative Morbidity

A total of 5 intraoperative complications occurred during the 71 total LS-HIPEC procedures (Table 2). Arrhythmias, including atrial flutter and sinus bradycardia, occurred during two procedures. Splenic bleeding occurred once, and outflow catheter obstruction occurred in two procedures, resulting in interruption of LS-HIPEC perfusion. No patients were converted from laparoscopy to laparotomy for any reason.

Overall, clinically significant (Clavien-Dindo grades III/IV/V) per-procedure complications within 30 days were low, with only one grade III complication resulting in a diaphragmatic injuring leading to pneumothorax requiring tube thoracostomy. There were no deaths in the cohort (Clavien-Dindo grade V).

Adverse Events/CTCAE Toxicity

Toxicity following the 71 LS-HIPEC procedures is detailed in Table 3. Clinically significant grade 3 or 4 toxicity occurred in a minority of patients. The only grade

TABLE 1 Patient demographics, disease and treatment characteristics

	Patients	LS-HIPEC procedures
Total	44	71
Age, median (range)	56.5 (30–75)	57 (30–75)
Female, *N* (%)	16 (36)	24 (34)
No. of LS-HIPEC Procedures	1 (1–5)	
Primary tumor location, *N* (%)		
GE junction	13 (30)	22 (31)
Body	10 (23)	20 (28)
Antrum	9 (20)	11 (15)
> 2 sites/diffuse	12 (27)	18 (25)
Lauren type, *N* (%)		
Diffuse	20 (45)	28 (39)
Intestinal	5 (11)	6 (8)
Mixed	1 (2)	1 (1)
Indeterminate	18 (41)	36 (51)
Preoperative therapy		
Chemotherapy, *N* (%)	44 (100)	71 (100)
No. of cycles, median (range)	8 (3–53)	8 (3–53)
Chemoradiation	20 (45)	29 (41)
Body surface area (m^2), median (range)	1.9 (1.27–2.65)	
Mitomycin-C/BSA, median (range)		15.9 (11.32–23.62)
Cisplatin/BSA, median (range)		105.9 (0–157.5)
Indication, *N* (%)		
Peritoneal cytology	14 (32)	
Carcinomatosis	30 (68)	
Malignant ascites	3 (7.8)	
Length of stay days, median (range)		2 (2–11)

TABLE 2 Per-procedure intraoperative complications

Complication	*N* (%)
Atrial flutter	1 (1.4)
Sinus bradycardia	1 (1.4)
Splenic bleeding	1 (1.4)
Outflow catheter obstruction	2 (2.8)
Conversion to laparotomy	0 (0.0)

4 toxicity was severe thrombocytopenia requiring platelet transfusion. Minor (grade 1–2) gastrointestinal toxicity occurred following 35% of LS-HIPEC procedures, whereas minor leukopenia occurred after 25%, and neutropenia after 9%. No LS-HIPEC procedures resulted in renal toxicity.

Gastrectomy Following LS-HIPEC

During the study period, 11 patients (25%) underwent gastrectomy following LS-HIPEC. Gastrectomy was performed following a median of 1 LS-HIPEC procedures (range 1–2). The majority of patients underwent total gastrectomy (n = 6, 14%), whereas 9% underwent subtotal gastrectomy (n = 4). One patient underwent Ivor-Lewis esophagectomy (1.4%). The majority of these patients (n = 10, 91%) underwent gastrectomy following resolution of low-volume carcinomatosis and with negative washings. Thus, these patients underwent gastrectomy with potentially curative intent and to prolong survival. One patient had known ovarian metastases and underwent gastrectomy along with bilateral salpingo-oopherectomy. A total of five patients underwent gastrectomy with intraoperative HIPEC as part of their surgical therapy.

DISCUSSION

In this study, we characterized perioperative outcomes and morbidity following 71 LS-HIPEC procedures performed in 44 patients with gastric or gastroesophageal adenocarcinoma with either peritoneal carcinomatosis or positive peritoneal cytology. Overall, LS-HIPEC was safe with low-grade III/IV 30-day morbidity (1.4%) and CTCAE toxicity (12.7%). The majority of morbidity and toxicity was mild, grade 1, and related to gastrointestinal symptoms.

Current guidelines by the National Comprehensive Cancer Network for patients with gastric adenocarcinoma with involvement of the peritoneal cavity are systemic chemotherapy or best supportive care. Prognosis for these patients is poor and contemporary management is nonsurgical.[11] However, the emerging data presented reveal LS-HIPEC as a therapeutic alternative suitable for further clinical investigation and also may allow for studies of the indications for proceeding with gastrectomy. A phase II trial from our institution of neoadjuvant LS-HIPEC for 19 gastric cancer patients with peritoneal involvement revealed a median overall survival (OS) from date of diagnosis of metastatic disease of 30.2 months and 20.3-month median OS from time of first LS-HIPEC procedure.[12] Although the selection of patients responding to chemotherapy likely contributed to this survival, this trial is encouraging given the reported median survival for patients with gastric adenocarcinoma involving the peritoneal cavity is 6–15 months.[2,11,13,14] Appropriate application of LS-HIPEC for these select patients requires the procedure to be a low-morbidity procedure, which is supported here.

The use of HIPEC following gastrectomy for patients with high-risk resectable gastric cancer has been supported by prospective trials, with improvement in survival for patients with serosal invasion and regional nodal metastases.[15,16] However, the addition of HIPEC to gastrectomy introduces further risk of significant complications, with reported morbidity rates of 15–53% and mortality 0–7%.[17,18] Potential downstaging, direct treatment of tumor deposits, and washing away of free cancer cells makes HIPEC an attractive option for patients with peritoneal dissemination of gastric cancer. Harnessing these theoretical beneficial effects of HIPEC in the neoadjuvant setting may result in both a decrease in morbidity following gastrectomy and better selection of patients to undergo surgery based on tumor biology. Further prospective and comparative studies are required to discern the impact of this strategy on survival for these patients.

TABLE 3 Per-procedure adverse events classified according to CTCAE ver. 4.0

Toxicity	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Leukopenia	11 (15)	7 (10)	2 (3)	0 (0)
Neutropenia	2 (3)	4 (6)	4 (6)	0 (0)
Thrombocytopenia	4 (6)	3 (4)	2 (3)	1 (1)
Renal	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal	22 (31)	3 (4)	0 (0)	0 (0)

Our results suggest that the application of LS-HIPEC in the neoadjuvant setting is safe, with low rates of clinically significant morbidity. In a study of the effects of neoadjuvant LS-HIPEC on reducing PCI levels before CRS, Yonemura and colleagues also reported a low rate of morbidity with this strategy.[19] In a systematic review that included 8 studies of 183 patients who underwent LS-HIPEC, Facchiano and colleagues found only 13 minor complications attributable to the procedure and the majority of these were in patients who underwent LS-HIPEC for palliation of malignant ascites.[8] Moreover, the authors report a 95% success rate for LS-HIPEC as a treatment of malignant ascites. All three patients with malignant ascites underwent only one LS-HIPEC procedure and unfortunately died shortly thereafter with reaccumulation of ascites. Therefore, further studies will be required to determine if LS-HIPEC is an effective palliative treatment option. Although only five patients in the Facchiano study underwent LS-HIPEC as a neoadjuvant treatment, the neoadjuvant approach to HIPEC for gastric patients is a particular strength of our study, and the low rate of significant morbidity supports the use of this strategy for patients with peritoneal involvement of gastric cancer.

Figure 1 demonstrates our proposed integration of LS-HIPEC into the care algorithm for patients with gastric adenocarcinoma metastatic to the peritoneum. Once confirmed carcinomatosis or positive intraperitoneal cytology is identified, patients undergo first-line chemotherapy followed by restaging. At this point following multidisciplinary discussion, if the patient has stable or improved disease without extraperitoneal dissemination, the patient is a candidate for LS-HIPEC with the regimen described herein. This can be repeated, or the patient may be dispositioned to gastrectomy with CRS + HIPEC or further systemic therapy. The optimal approach for these patients to undergo definitive surgery following LS-HIPEC in this algorithm will hopefully be elucidated in a phase II study initiated at our institution (NCT02891447).[9]

The majority of patients who underwent LS-HIPEC in this study had low-volume peritoneal carcinomatosis versus isolated positive peritoneal cytology (Table 1). Eleven patients (25%) proceeded to definitive resection, ten (91%) of who underwent gastrectomy with curative intent following documented absence of carcinomatosis and peritoneal cytology on subsequent diagnostic laparoscopy. This is encouraging, considering without this management strategy these patients would be dispositioned to nonsurgical management according to contemporary guidelines.[20] With low morbidity attributable to LS-HIPEC as reported here, repetitive procedures could be performed as long as patient performance status permits to achieve definitive resection. Addition of HIPEC at the time of definitive resection was performed in five patients, which will be evaluated in the treatment arm of a clinical trial.[9]

This study has several limitations. Our patient cohort is heterogeneous, with patients with both gastric and gastroesophageal junction tumors, a varying range of tumor sizes, and patients with positive peritoneal cytology, low-volume carcinomatosis, or both. Moreover, there was no standardized, preoperative therapy regimen, and thus it is reasonable to submit that local and occult systemic disease control was heterogeneous. However, as a referral center many patients receive first-line systemic therapy at outside institutions before presenting to M.D. Anderson Cancer Center. The retrospective nature of our work is another limitation; however, prospective data collection and clinical trials incorporating LS-HIPEC into the treatment paradigm of patients with gastric cancer are ongoing.

CONCLUSIONS

LS-HIPEC is safe and can be repeated for patients with peritoneal involvement by gastric cancer and may lead to gastrectomy. Much morbidity following LS-HIPEC is minor, and further studies evaluating various therapy regimens and timing in relation to systemic therapy may result in increased tolerance and thus further procedures until resolution of cytology and carcinomatosis. Ongoing prospective trials evaluating LS-HIPEC followed by gastrectomy with intraoperative HIPEC will aid in optimal incorporation of this novel technique into the treatment of patients with Stage IV gastric adenocarcinoma.

DISCLOSURE No conflicts of interest to disclose.

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